

Structural Characterization of the Catalytic Active Site in the Latent and Active Human Gelatinase B from Neutrophils

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Breakdown of the extracellular matrix is an important event in many normal and pathological processes in the body, such as growth, wound repair, tumor metastasis and arthritis. A large family of zinc-dependent proteinases, the matrix metalloproteinases (MMPs), is considered to be primarily responsible for this matrix catabolism. The MMPs family members share many common structural and functional elements even though they stem from different genes. MMPs are initially secreted by the cell in a non-active form (zymogen). Previous studies led to the formulation of the "cysteine switch hypothesis" as a model for understanding the unique structure of MMP zymogenes and the means by which activation may be achieved *in vitro*. The cysteine switch model suggests that upon activation, the latent zinc-binding site convert to a catalytic zinc-binding site by dissociation of the thiol-bearing propeptide from the zinc atom. This makes the metal ion and the active site pocket accessible for substrate binding.

Several studies have suggested that the isolated MMPs catalytic domain contain two zinc atoms that are required for enzyme stabilization and catalysis. Recent publications and our results suggest that the intact full length MMPs contain only a single zinc-atom. We report here the X-ray absorption spectroscopy (XAS) studies of the catalytic active site of the monomeric form of natural human gelatinase B in its latent and activated state. Our results demonstrate the rearrangement and conformational changes that occur upon catalysis in human gelatinase B.